COMMENTARY

Hormone-associated Cancer: Mechanistic Similarities between Human Breast Cancer and Estrogen-induced Kidney Carcinogenesis in Hamsters

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Estrogens are risk factors for human breast cancer and induce kidney tumors in Syrian hamsters. Mechanistic features of the estrogen-induced hamster kidney tumor model have been compared with corresponding aspects of human breast cancer to gain insight into the mechanism of human mammary oncogenesis. Shared characteristics point to a mechanism of metabolic activation of steroidal estrogens to 4-hydroxylated catechol metabolites that may undergo metabolic redox cycling, a mechanism of generation of reactive free radicals. Tumors may arise in cells genetically altered by various types of estrogen-induced DNA damage. At the same time, these altered cells may respond to estrogen receptor-mediated stimuli in support of cell transformation and growth. — *Environ Health Perspect* 105(Suppl 3):565–569 (1997)

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Estrogens and Breast Cancer

Estrogen administration is accepted by most epidemiologists as a risk factor of human endometrial adenocarcinoma (*1,2*). Thus, estrogens unopposed by progestins increase the risk of uterine tumors. This risk increases with increasing doses of estrogen and with the length of treatment (*3*). Obesity also increases uterine tumor risk, most likely because the aromatase activity of adipose cells elevates circulating estrone levels (*3,4*).

Increasing evidence shows that elevated levels of estrogens in the body are also a risk factor in breast cancer. Exogenous estrogens, alone or in combination with progestin, elevate breast cancer risk (*5–7*). Progestin added to the estrogen medications does not inhibit mammary carcinogenesis (*8*) because the former hormone appears to be the primary mitogen of mammary ductal epithelial cells (*9*), whereas estrogen appears to function in this manner in the uterus. This role of estrogen in human breast carcinogenesis is supported by risk factors of breast cancer such as high serum or urine estrogen levels (*10,11*), the early onset of menstruation, or late menopause (*12*). These relationships are illustrated by the fact that the breast cancer risk of a woman undergoing menopause at 45 years of age is half that of a woman experiencing menopause at 55 years of age (*5,6,12*). These lines of evidence indicate that the total lifetime exposure of a woman to exogenous or endogenous estrogen is a determinant of her breast cancer risk.

Animal Models of Estrogen-induced Cancer

For the examination of the mechanism of estrogen-induced tumorigenesis, animal models are needed in which steroidal estrogens induce tumors with high incidence. There are very few reports in rodent models of estrogen-induced mammary tumorigenesis not mediated by hydrocarbon carcinogens, viruses, or other initiating agents. Estrogens induce or enhance tumor formation in organs of rodents such as the uterus (*13,14*), pituitary (*15,16*), prostate (*17*), uterine cervix (*18*), testes (*19*), and liver (*20*). In addition, the estrogen-induced kidney tumorigenesis in Syrian hamsters has been used extensively for mechanistic studies (*21*) because 100% tumor incidence is routinely achieved using the natural hormone 17β-estradiol (E_2) or estrone without coadministration of any other carcinogens. This animal model is useful for mechanistic studies because the tumor is estrogen induced and estrogen dependent, because cell lines have been developed that share growth characteristics with the primary tumor (*22,23*), and because the tumor incidence may be manipulated by coadministration of other hormones such as progesterone or testosterone (*21*).

Several synthetic steroidal estrogens were only weakly carcinogenic in this model system despite their powerful hormonal potencies (*21,24,25*). This lack of correlation of estrogenic characteristics with carcinogenic activities of steroids led to the conclusion that hormonal potency of an estrogen was necessary but not sufficient for tumor induction (*24,25*). It was further concluded that metabolic activation of estrogens to reactive intermediates is a key event in the development of estrogen-induced tumors.

Mechanism of Estrogen-induced Carcinogenesis in Hamsters

The metabolic activation of estrogens to catechol metabolites and further to reactive semiquinone or quinone intermediates is a central feature of this mechanistic proposal and is analogous to the metabolic activation of many other carcinogens. The primary metabolic conversion of the estrogenic hormones estrone or E_2 in liver of most mammalian species is 2-hydroxylation, as shown for hamsters in Table 1 (*26,27*). However, an elevated formation of 4-hydroxyestrogen metabolites by specific estrogen-4-hydroxylases has been detected in hamster kidney (*28*), mouse uterus (*29*), and rat pituitary (*30*)—all organs in which estrogens are known to induce tumors (*13–16,21*). The elevated formation of 4-hydroxyestrogens in rodent organs in which estrogens induce tumors is significant because catecholestrogens, including 4-hydroxyestrogens, may undergo

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Abbreviations used: E_2, 17β-estradiol; LHP, lipid hydroperoxides; 2-OH-E_2, 2-hydroxyestradiol; 4-OH-E_2, 4-hydroxyestradiol.

Table 1. Microsome-mediated conversion of 10 μM E_2 to catechol metabolites in targets of estrogen-induced cancer and controls.[a]

Target	2-OH-E_2, pmol/mg	4-OH-E_2, protein/min	4-OH-E_2/2-OH-E_2	Reference
Hamster liver control	365.0	52.4	0.14	Weisz et al. (*28*)
Hamster kidney				
Control	13.4	7.2	0.5	Weisz et al. (*28*)
E_2-Treated	2.2	6.1	2.8	
CD-1 mouse uterus				
Control	0.1	1.3	13.0	Paria et al. (*29*)
Sprague-Dawley rat pituitary				
Control	0.03	0.29	9.7	Bui and Weisz (*30*)
E_2-Treated	0.08	0.24	3.0	

[a]Ratios of 4-OH-E_2/2-OH-E_2 in hamster liver are comparable to those in other mammalian species (*26,27*).

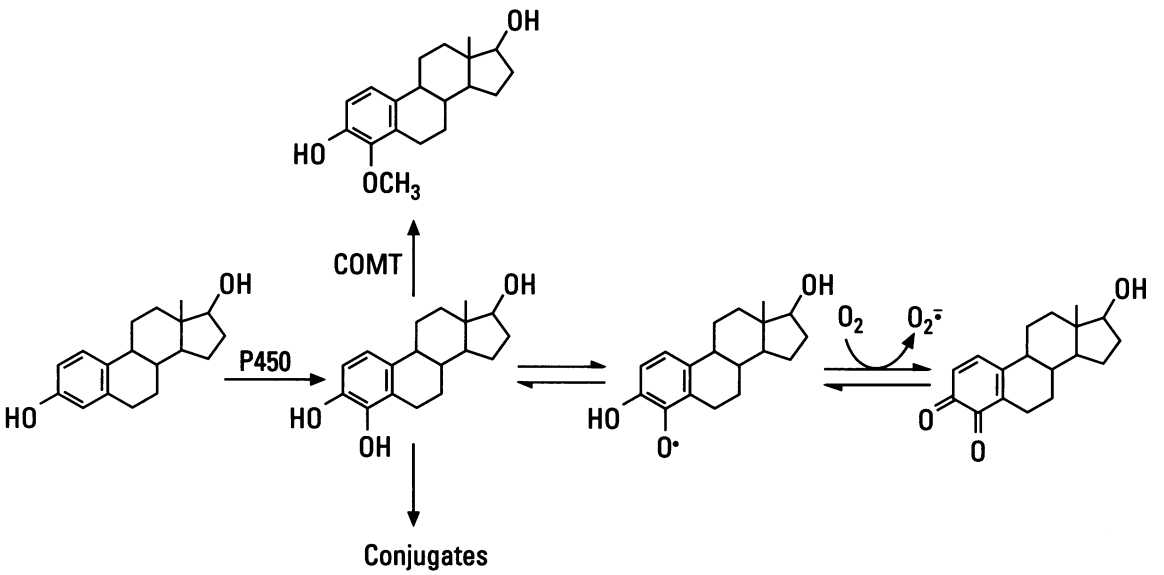

Figure 1. Formation and redox cycling of 4-OH-E_2. E_2 is converted by cytochrome P450 enzymes, including P4501B1, to 4-OH-E_2, which may undergo metabolic redox cycling between hydroquinone and quinone forms via semiquinone intermediates. The oxidation of this cycle is catalyzed mainly by organic hydroperoxide-dependent cytochrome P4501A1 and the reduction by NADPH-dependent cytochrome P450 reductase. The semiquinone is a free radical that may react with molecular oxygen to form superoxide. Detoxification pathways are phase II conjugation reactions of the catechol, including methylation by catechol-*O*-methyltransferase (COMT). Details are outlined in a recent review by Yager and Liehr (*54*).

metabolic redox cycling between hydroquinone and quinone forms (Figure 1).

The catecholestrogen quinone intermediates may form covalent DNA adducts (*31,32*). Moreover, metabolic redox cycling generates free radicals that are capable of direct or indirect covalent modification of DNA (Figure 2) (*33,34*). In line with this hypothesis, hydroxy radical damage such as 8-hydroxyguanine bases of DNA or DNA single strand breaks have been detected in the kidney of hamsters treated with estradiol (*35–37*). In addition, intranuclear, site-specific redox cycling involving catecholestrogen metabolites and copper ions may induce DNA damage by reactive oxygen, which is not mediated by metabolizing enzymes (*38*).

Lipid hydroperoxides (LHP) play a central role in the DNA damage process by catechol estrogens (Figure 2). LHP are formed by free radicals generated by redox cycling. They, in turn, support redox cycling as cofactors in the cytochrome P4501A-mediated oxidation step of the redox cycle (*33,39*). Finally, LHP may decompose into reactive aldehydes such as malondialdehyde, which covalently bind to DNA (*40*).

One or several of these classes of covalent DNA damage may initiate and/or promote the carcinogenic process (Figure 3). Tumors may develop from cells genetically altered by the processes outlined above. At the same time, these altered cells may respond to a receptor-mediated proliferative stimulus either by estradiol or by 4-hydroxyestradiol, which is known to be a long-acting estrogen (*41*).

Mechanistic Analogies in Hamster and Human Breast

Despite the obvious differences arising from the differences of organ system, cell type, latency of tumor development, and other factors, there are several common features of estrogen-induced kidney tumors in hamsters and human breast cancer (Table 2), that point to the mechanistic pathway outlined above as a possible explanation of human mammary oncogenesis. Elevated urinary or serum estrogen levels in women at risk of breast cancer indicate an inducing role of estrogen in the carcinogenic process

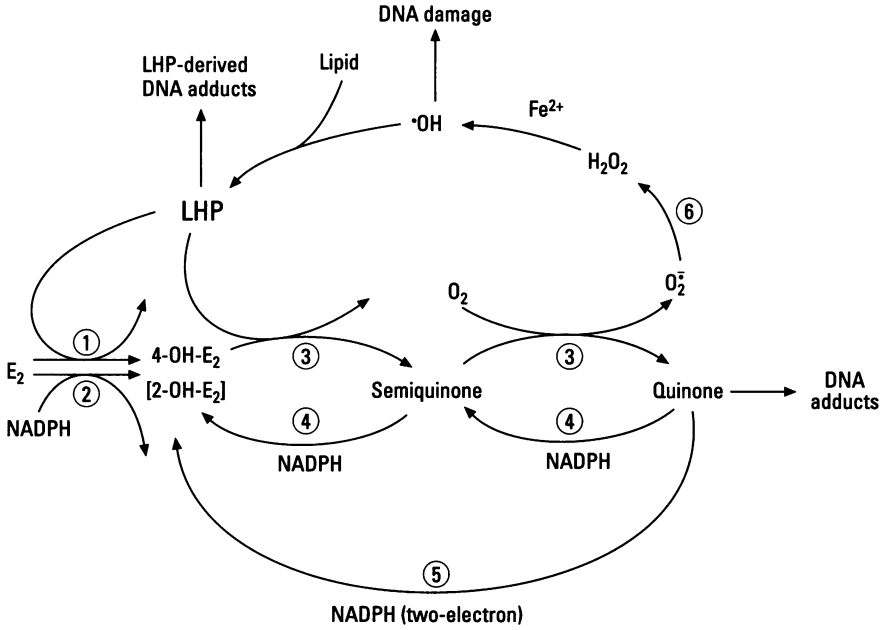

Figure 2. Proposed pathways of DNA damage by metabolic activation of estrogens. In target tissues, the natural hormone E_2 may be converted by NADPH- or LHP-dependent pathways (1 or 2, respectively) predominantly to 4-OH-E_2. This catecholestrogen metabolite may undergo metabolic redox cycling by LHP-dependent oxidation to the semiquinone and quinone catalyzed by cytochrome P4501A family enzymes (3). The quinone may be reduced by NADPH-dependent cytochrome P450 reductase (4) or by NADH-dependent quinone reductase (5) in a two-electron reduction bypassing the semiquinone. The semiquinone may react with molecular oxygen to form superoxide radicals, which are reduced to hydrogen peroxide by superoxide dismutase (6). H_2O_2 may be reduced by metal ions to hydroxy radicals, which initiate the formation of LHP. DNA may be covalently modified by aldehyde decomposition products of LHP, by hydroxy radicals, or by covalent binding of quinone metabolites. Although 2-OH-E_2 (in brackets), the most common metabolite formed by liver enzymes, is capable of undergoing metabolic redox cycling, its contribution to free radical generation and DNA damage may be negligible because it is converted to conjugates by phase II metabolism enzymes much more efficiently than the 4-hydroxylated isomer. The potential of estrogen metabolites to damage cells is potentiated by redox cycling and by the initiation of free radical reactions. Details of this pathway are outlined in a recent review by Yager and Liehr (*54*).

Table 2. Shared characteristics of human breast cancer and estrogen-induced hamster kidney tumorigenesis.

Mechanistic features	Human breast, reference	Hamster kidney, reference
E_2 as risk factor/inducing agent	Toniolo et al. (*10*); Adlercreutz et al. (*11*); Henderson et al. (*12*)	Kirkman (*21*)
Specific 4-hydroxylation of E_2	Liehr and Ricci (*43*)	Weisz et al. (*28*)
Increased 8-OH-dG bases in DNA	Malins et al. (*47*)	Han and Liehr (*36,37*)
Single strand breaks of DNA	Nutter et al. (*53*)[a]	Han and Liehr (*35*)
Elevated LHP levels	Boyland and McGuire (*48*)	Wang and Liehr (*39*)
Increased malonaldehyde–DNA adducts	Nath et al. (*49*); Wang et al. (*50*)	Wang and Liehr (*40*)
Tumor incidence decreased by vitamin C	Howe et al. (*51*)	Liehr and Wheeler (*52*)

[a]The induction of DNA single strand breaks by an estrogen metabolite has been demonstrated in MCF-7 breast cancer cells (*53*).

(*10,11*). However, not every woman with high estrogen levels will develop this disease. Thus, an estrogen metabolite rather than the parent hormone likely is the ultimate carcinogenic factor. This reasoning is supported by the elevated urinary catecholestrogen concentrations in women at risk of breast cancer compared to controls (*11*). Moreover, in microsomes of MCF-7 breast cancer cells (*42*) and of human mammary fibroadenoma and adenocarcinoma (*43*), 4-hydroxylation of estradiol strongly predominated over 2-hydroxylation. This formation of 4-hydroxyestrogens in humans is mediated by a specific enzyme activity, cytochrome P4501B1 (*42,44,45*).

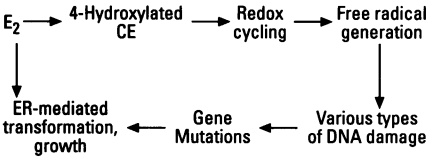

Figure 3. Proposed mechanism of estrogen-induced carcinogenesis. E_2 is activated by hydroxylation to 4-hydroxylated catecholestrogens (CE), their redox cycling, and free radical generation as outlined above. The various types of DNA damage generated by metabolic activation of estrogens may induce gene mutations. Tumors are proposed to arise in cells genetically altered by this estrogen-induced genotoxicity. At the same time, these altered cells may respond to ER-mediated cell transformation and growth.

Thus, in target cells of mammary oncogenesis, estradiol may be preferentially converted to 4-hydroxyestradiol, which in the hamster kidney tumor model is a carcinogenic metabolite of estradiol (*46*). Consistent with the pathway of metabolic activation and DNA damage outlined above, elevated levels of 8-hydroxyguanine bases of DNA (*47*), increased lipid peroxidation (*48*), and increased levels of LHP-derived aldehyde DNA adducts (*49,50*) have been detected in mammary tissues of breast cancer patients. The same indicators of indirect, estrogen-induced cell damage have been detected previously in hamsters and are listed in Table 2. Consistent with a hypothesis of tumor initiation by estrogens, vitamin C decreased mammary tumor incidence in humans (*51*), as has been observed previously in hamsters (*52*).

Conclusion

Complex interactions of metabolic, chemical, physiological, and endocrine effects of estrogenic hormones are involved in the induction of tumors in the breast. This complexity requires a multidisciplinary design of experiments because emphasizing various aspects of carcinogenesis has not sufficed to explain the full sequence of events resulting in the appearance of mammary tumors. The mechanisms outlined above are complex and difficult to understand, yet represent the best explanation to date of the experimental data. Additional research into better animal models, into the relation of estrogen metabolism to breast cancer, and into better assays of estrogen metabolites and metabolizing enzymes will provide a more detailed understanding of mammary carcinogenesis.

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